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PhRMA

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Docket 00D-1350 - *FDA Draft Guidance for Industry Combined Oral Contraceptives - Labeling for Healthcare Providers and Patients* (65 Federal Register 42387, 10 July 2000)

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Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is submitting this set of comments on the " Draft Guidance for Industry Combined Oral Contraceptives - Labeling for Healthcare Providers and Patients."

PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. PhRMA member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives; our members invest over $26 billion annually in the discovery and development of new medicines. For this reason, PhRMA and its member companies are keenly interested in all aspects of the drug development process, including the format and content of labeling for healthcare providers and patient instructions for use of Combined Oral Contraceptives that contain estrogen and progestin (COCs). We endorse the concept of providing prescribers and patients with consistent labeling that describes the benefits and risks associated with products in this class, while also allowing for any information that may be unique to individual products. We appreciate the opportunity to provide comments on the draft guidance.

The following comments are grouped into general comments on the guidance as a whole, followed by specific comments on various sections of the document.

General comments

The stated purpose of the FDA's draft guidance document, which is an update of a 1994 version, is to guide Sponsors when they propose labeling for COCs in NDAs/ANDAs. However, the Federal Register notice states that, "Once the draft guidance is finalized, the recommended text should be included in all approved, pending, and future applications" and "When finalized the guidance should result in uniform labeling among combined oral contraceptive products." Thus, the draft guidance document suggests that it will be applied only to new marketing applications, whereas the notice states that existing products would be subject to labeling changes based on the guidance. This should be clarified in the guidance.

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While we agree with the concept of providing consistent labeling, caution should be used when considering changes in labeling for marketed products with well-established use profiles. PhRMA believes that prescription drug labeling, in its current format and with the current content presented in 21 CFR 201.57, succeeds in providing adequate directions for use of drug products. Retroactive application of labeling revisions for COCs should be required only on a case-by-case basis, as appropriate, and with agreement between the manufacturer and the Agency. PhRMA recommends that the Introduction of the draft guidance document be expanded to provide a clear indication of the scope and intended application of the guidance.

The labeling templates presented in the draft document are intended to address information needs of both patients and health care providers, but, in PhRMA's opinion, the resulting labeling would be too long and complicated for patients. Further, while it is admirable to try to develop a simpler, yet complete set of instructions for patients, PhRMA strongly urges FDA to subject the draft document to health literacy criteria assessment and also to specifically seek input from other stakeholders (e.g., professional medical societies, patient advocacy groups, etc.).

With only two exceptions, references supporting the proposed changes to the labeling were not provided with the draft guidance. This did not allow for a thorough assessment of the proposed changes, as PhRMA could not analyze the information FDA used to develop the changes. The current practice of providing a list of references in the labeling should remain. Furthermore, it is imperative that the Agency provide the references used in support of statements made in the current draft guidance.

PhRMA asks that the Agency provide a formal comment period for drafts of the PATIENT PACKAGE INSERT, the BRIEF PATIENT SUMMARY, and the DETAILED PATIENT SUMMARY, if still relevant.

Specific comments

1. **Warning – Cigarette Smoking (Guidance page 1)**

   We recommend that the term "quite marked" be replaced with more descriptive information, such as a statement regarding actual risk.

2. **Emergency Contraception (Guidance page 3, Table 1)**

   Table 1 now contains an endnote regarding "Emergency Contraceptive Pills," which refers to table footnote 9 containing a list of branded oral contraceptives that FDA has declared safe and effective for emergency contraception (62 Federal Register 8612; February 25, 1997) following a 1996 Advisory Committee meeting. PhRMA questions whether non-approved, "off-label" uses should be included in product labeling and believe that it is not appropriate to include dosing recommendations for other manufacturers' products in another's label. However, if it is deemed appropriate to include reference to use of these products for Emergency Contraception, then safety information relevant to this use must also be provided in

the label. If provided, the information on Emergency Contraception should not be included as part of Table 1, but under a separate heading in the text (e.g., "What To Do In Case of Failure") with references. In addition, the list provided in the draft guidance should be reviewed for completeness, including identification of product(s) that may be approved and indicated for this purpose.

3. Failure rates (Guidance page 3, Table 1)

The unintended pregnancy (failure) rates shown in Table 1 should include the full range of rates experienced and reported in the scientific literature. The literature indicates that, in some populations, failure rates may approach 27% with COCs (Jones & Forrest, Contraceptive Failure Rates Based on the 1988 National Survey of Family Growth. Family Planning Perspectives **24**:12-19, 1992). However, a recent study from Norway suggests that only one-third of failures among women terminating their pregnancy should be attributed to method failures (Skjeldestad, Oral Contraceptive Failures Among Women Terminating Their Pregnancy. Acta Obstetricia et Gynecologia Scandinavica **79**:580-585, 2000).

"Female Sterilization" should be listed as "Surgical Sterilization – Female" and failure rates should be stratified by procedure type, e.g., tubal ligation, etc. (Westhoff and Davis, Tubal Sterilization: Focus on the U.S. Experience. Fertility & Sterility **73**:913-922, 2000). Likewise, reference to "Male Sterilization" should be clarified as to surgical, chemical, etc.

4. Contraindications, Warnings, Precautions, and Adverse Experiences Sections (Guidance pages 4-11)

PhRMA is concerned that, when compared with the 1994 version, significant changes were made to these sections without references. Examples of such changes are:

- The addition of new diseases
- The deletion of information previously contained in these sections
- The broadening and narrowing of disease categories
- Changing the ordering of various Contraindications, Precautions, Warnings and Adverse Events Sections, implying a downgrade in importance

The full impact of these changes was difficult to determine, since references for the underlying data or other information (e.g., literature citations) used to support them were not provided. We acknowledge that certain of the proposed changes to particular product labeling may be appropriate and provide important, updated safety information to the extent supported by substantial evidence on a product-by-product basis. Not all such information will be generalizable to COCs as a class.

5. Pediatric Use (Guidance pages 7 and 10)

There appears to be a conflict regarding proposed statements on safety in the pediatric population. As currently stated, wording in the Warnings section (page 7, Warning 7) implies that there is an elevated risk of breast cancer in women who first

used COCs before age 20. This appears to conflict with wording in the Precautions section concerning Pediatric Use (page 10, Precaution 9), which states that safety is expected to be the same for women of all ages. PhRMA recommends that this conflict should be resolved and the risk clearly and accurately stated in the appropriate section(s).

6. Drug Interactions (Guidance page 9, Precaution 3)

PhRMA agrees with the Agency on the importance of including information on potential drug interactions for health care providers and patients. This information must be accurate and complete. It is important, therefore, that the reasons for concern with the listed drugs be given. For example, the concomitant use of ascorbic acid is mentioned as resulting in increased ethinyl estradiol levels. However, the effect of sudden withdrawal of ascorbic acid may result in a rebound decrease in levels of ethinyl estradiol.

There appears to be a contradiction in the advice given to patients regarding antibiotics (guidance pp. 9 and 17). A back-up method of contraception is recommended for patients who are prescribed antibiotics, but health care providers are advised that concomitant antibiotics are not a problem (except for rifampin). Other data for antimicrobial compounds not shown in the draft guidance may be available and should be considered for inclusion in the interactions subsection. See Shenfield, Oral Contraceptives: Are Drug Interactions of Clinical Significance? Drug Safety **9**:21-27,1993; Burroughs and Chambliss, Antibiotics and Oral Contraceptive Failure. Archives of Family Medicine **9**:81-82, 2000; and Barditch-Crovo, Trapnell, Ette, et al, The Effects of Rifampin and Rifabutin on the Pharmacokinetics and Pharmacodynamics of a Combination Oral Contraceptive. Clinical Pharmacology and Therapeutics, **65**:428-438, 1999.

The reference to troglitazone should be deleted, as this product is no longer marketed. PhRMA hopes the Agency finds these comments useful and constructive. We would be pleased to discuss these comments with you in person or via teleconference, at your request. PhRMA welcomes future opportunities to continue to work with the Agency to formulate a new framework for communicating information on product labeling related to combined oral contraceptive products.

Sincerely,

Alan Goldhammer